



Joint UNICEF - UNAIDS - WHO/EDM - MSF Project

Selected drugs used in the care of people living with HIV: sources and prices.

October 2000

Introduction

Treatment for HIV-related conditions is limited in developing countries. Reasons include limitations in infrastructure for diagnosis and treatment, lack of epidemiological data on the patterns of opportunistic diseases necessary to plan treatment interventions, gaps in the supply system, and the high cost and poor ability to finance the purchase of drugs. To improve access to drugs used in HIV-related conditions, the WHO Expert Committee on the Use of Essential Drugs included in the tenth and eleventh Model List of Essential Drugs a number of drugs used to treat opportunistic infections of special importance in HIV/AIDS. However, most of them were not included in the range of products distributed by international generic suppliers, and access to them remained limited in developing countries. The availability of comparative price information for these drugs was also very limited.

To find supply solutions for these drugs, UNAIDS, UNICEF and WHO initiated a joint project that specifically sought to identify suppliers and supply-related information. MSF joined the project in 2000. The outcome of this project is a database containing information relevant to drug procurement for use by countries and donors to improve access to HIV/AIDS-related drugs. The project did not intend to assess and pre-qualify suppliers: procurement agencies should follow their own procedures in this respect.

Drug selection and sources

The products included in the project are 34 active ingredients, present in 63 pharmaceutical presentations. They include essential drugs used to treat opportunistic infections and HIV-related malignancies. In contrast to the first report (February 2000), this report also includes several antiretroviral drugs.

Over two hundred companies from a total of 40 countries which had products licensed in their respective countries were contacted. Only 34 of these from 16 countries replied with complete information. The information requested included: registration status of the product in the country of origin, information on production capacity and lead times,

indicative prices in the country of origin and possession of manufacturing license and GMP certificate* issued by their respective National Drug Regulatory Authorities. Only companies that forwarded the requested documentation were included, as this was the basis for screening the suppliers and products.

While all attempts were made to contact as many manufacturers as possible, the list remains incomplete and is open to further additions. Additionally, some drugs are the subject of patents in some countries, precluding the introduction of generic alternatives in those countries. This matter is country specific and must be addressed at national level.

The database will continue to be kept up to date and further reports will be made available when relevant.

Supply and prices

The data collected during the study show that the majority of drugs are available as generics on the international market. Prices vary widely, but realistic indicative prices for bulk procurement can be estimated for many products. The limitations of these 'indicative' prices are:

- a) Prices apply generally in the context of bulk procurement i.e. the working unit is one batch. Batch sizes vary greatly among formulations and manufacturers, but the following sizes are typical: capsules and tablets, 100,000 to 500,000 (batches of over 1 million are not uncommon, but these are not minimum purchases); vials and bottles, 5,000 to 20,000.
- b) Prices are ex-works (EXW) or free-on-board (FOB). Freight, insurance and taxes are not included.
- c) Manufacturers may have contractual agreements or different pricing structures for specific countries. These factors are not included in the study.

In most cases, these indicative prices are a fraction of the prices often used in comparisons, such as those published in the British National Formulary.

The following information is provided for each drug:

- 1- General comments on availability and cost.
- 2- Inclusion in the WHO Model List of Essential Drugs (11th revision, December 1999).
- 3- For each therapeutic class, price of drugs (with their range, median and 25th percentile of the price distribution), as supplied by the manufacturers, the number of manufacturers that gave indicative prices, and, for comparison, two list prices from the UK and Spain. For these two list prices the lowest price among bioequivalent products is shown, with no differentiation among original or generic products. The difference in costs of drugs between the British and the 25th percentile price taken from the survey is added for examples for treatment of HIV-related conditions. This illustrates the potential of using the information gathered in this survey.

* In accordance with WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, 1996.

Further information and contacts

Outputs of the database include: (a) product information related to availability, cost and shelf life, (b) range of indicative prices of individual products, with examples of established and publicly available tender prices (if available) and (c) manufacturer contact information. Parts (a) and (b) are published in the present document and on the Internet and will be updated as new information is collected. Contact information for manufacturers can be supplied to government agencies and purchasing groups on request. Manufacturers interested in supplying information are also invited to contact the project.

1. DRUGS USED TO TREAT OPPORTUNISTIC INFECTIONS: FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION AND TREATMENT OF AIDS PATIENTS

1.1. ANTIBACTERIAL DRUGS

Ceftriaxone, Ciprofloxacin, Clindamycin, Sulfadiazine

Ceftriaxone

Ceftriaxone was added to the WHO Model List of Essential Drugs (MEDL) in 1995 as a reserve antibacterial. It is an important drug used in the treatment of sexually transmitted diseases and bacterial meningitis. However, its high price is an obstacle to accessing this drug (this applies also to other third generation cephalosporins).

Use in HIV/AIDS: Sexually transmitted infections (STI).

Notes in 11th Model list: Example of a therapeutic group. Reserve antimicrobial. To be used only when there is significant resistance to other drugs on the list.

- **powder for injection, 250 mg (as sodium salt) in vial.** MEDL. Reported shelf-life: 36 months.

Ciprofloxacin

This broad-spectrum antimicrobial is included in the MEDL as an example of a therapeutic group (quinolones). It was added to the seventh list (1991) as a complementary antimicrobial to be used only in patients with infections resistant to other drugs in the List. In 1995, it was transferred to the main list. While it is accepted that wide use of fluoroquinolones is not advisable due to the development of resistance, the high price of ciprofloxacin is an obstacle to its utilization when it is needed.

Patented by Bayer in 1981 (Germany), ciprofloxacin has been available from other manufacturers in markets where it has not been patent protected. Most of the manufacturers that replied had carried out bioequivalence studies.

Use in HIV/AIDS: Treatment of bacterial infections, including salmonellosis and shigellosis. STI protocols.

Notes in 11th Model list: Example of a therapeutic group.

- **tablet, 250 mg.** MEDL. Reported shelf-life: 24 to 36 months.

Clindamycin

Clindamycin injection was added to the MEDL in 1991 as a complementary drug for use in patients allergic to penicillin and in infections resistant to other drugs in the main list. The capsules were added in 1997. The generic market for clindamycin is not very extended.

Use in HIV/AIDS: Treatment of *Pneumocystis carinii* pneumonia (PCP), treatment of toxoplasmosis.

Notes in 11th Model list: Complementary drug (when drugs in the main list are known to be ineffective or inappropriate for a given individual). Limited indications or spectrum of activity.

- **capsule, 150 mg.** MEDL. Reported shelf-life: 36 months.
- **injection, 150 mg (as phosphate)/ml.** Available in 2, 4 and 6 ml ampoules. MEDL. Reported shelf-life: 24 months.

Sulfadiazine

Sulfadiazine, developed in 1940, was added to the MEDL in 1997. Its inclusion, replacing sulfadimidine, was on the basis of its efficacy in the treatment of toxoplasmosis in combination with pyrimethamine. It is included in the list representing short-acting systemically-acting sulfonamides.

Largely an abandoned drug, it received renewed attention for the treatment of cerebral toxoplasmosis in AIDS patients. In 1992 there was a shortage of the drug in the USA, as the only manufacturer ceased operations. In 1994, it was reintroduced onto the market with orphan drug status, carrying a seven year period of exclusivity. In the USA, the Average Wholesale Price in 1991 was 3.10 USD for a pack of 100 tablets, but today the drug is 30 times more expensive (Average Wholesale Price 98.73 USD/pack of 100 tablets).

Sulfadiazine sodium injection is marketed in only a few countries, and its price is very high. Only one manufacturer was identified in the 1999 survey – in the 2000 survey this manufacturer did not respond.

The combination sulfadiazine-pyrimethamine-calcium folinate is considered as a first line treatment for cerebral toxoplasmosis. Treatment costs associated with this combination can vary widely depending on the price of any of the drugs (especially sulfadiazine and calcium folinate). An example of costs is presented in the description of antipneumocystosis and antitoxoplasmosis drugs (table 8).

Use in HIV/AIDS: Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis.

Notes in 11th Model list: Example of a therapeutic group. In renal insufficiency, contraindicated or dosage adjustments necessary.

- **tablet, 500 mg.** MEDL. Reported shelf-life: 48 to 60 months.
- **injection, 250 mg (sodium salt) in 4-ml amp.** MEDL.

Table 1. Sources and prices of antibacterial drugs

ANTIBACTERIALS	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Ceftriaxone										
inj, 250 mg in vial	6	3	vial	2.8	0.48	1.40	0.61	2	3.85	2.14
Ciprofloxacin										
tab, 250 mg	15	8	tab	0.95	0.02	0.10	0.04	5	1.05	0.37
Clindamycin										
cap, 150 mg	3	2	cap	0.94	0.08	0.27	0.17	1	0.64	-
inj, 150 mg/ml in amp	1	1	2-ml	1.40	1.40	1.40	1.40	1	6.95	-
Sulfadiazine										
inj, 250 mg in 4-ml amp.	-	-	amp	-	-	-	-	-	6.99	-
tab, 500 mg	5	5	tab	0.33	0.02	0.05	0.02	2	0.44	0.05

Explanatory notes to tables at the end of the document

1.2. ANTIFUNGAL DRUGS

Amphotericin B, Fluconazole, Itraconazole, Ketoconazole

Amphotericin B

Amphotericin B is marketed world-wide by Bristol-Myers Squibb. It is an essential drug for the treatment of cryptococcal meningitis and other life-threatening infections that affect people living with HIV. Although Amphotericin B is an old drug, its manufacture is difficult and there is no generic competition.

Use in HIV/AIDS: Cryptococcal meningitis, histoplasmosis and coccidioidomycosis, aspergillosis.

Notes in 11th Model list: In renal insufficiency, contraindicated or dosage adjustment necessary.

- **powder for injection, 50 mg in vial.** MEDL. Reported shelf-life: 24 months, REFRIGERATION REQUIRED.

Fluconazole

Introduced in the 1999 MEDL, fluconazole represents the group of triazole antifungal drugs. It replaced ketoconazole.

Pfizer holds the patents for this important fungicide, and the company's price policy has attracted a great deal of attention. In the USA, the patent expires in January 2004 (the patent expired originally in 2001 but the protection period was extended). The British and European patents were granted in late 1981 and January 1982. Fluconazole has also been at the centre of the market exclusivity/compulsory license debate, especially in Thailand and South Africa.

Presently, fluconazole capsules, tablets and solution for injection are produced by generic manufacturers in numerous countries where no product patent existed at the time the fluconazole patent was filed.

Use in HIV/AIDS: Treatment and prophylaxis of cryptococcal meningitis, treatment of oesophageal and resistant oropharyngeal candidiasis and vaginal candidiasis, treatment and maintenance of coccidioidomycosis.

Notes in 11th Model list: Example of a therapeutic group.

- **capsule/tablet, 200 mg.** Strength not in MEDL. Reported shelf-life: 24 to 36 months.
- **solution for injection, 2 mg/ml in bottle.** MEDL. Reported shelf-life: 24 to 36 months.

Itraconazole

Itraconazole is important in the treatment of certain fungal infections related to HIV/AIDS. Fluconazole, a member of the same family (triazoles), is included in the 1999 MEDL. Itraconazole is marketed in most countries only as a proprietary product and limited sources of generics exist. No generic producers of the oral solution were found.

Itraconazole has been patented mainly in industrialized countries. The patent has expired in many countries but an extension of the patent has been granted in France.

Use in HIV/AIDS: Treatment of resistant oral and oesophageal candidiasis, maintenance of cryptococcosis, treatment of histoplasmosis.

- **capsule, 100 mg.** Not in MEDL. Therapeutic group represented by fluconazole. Reported shelf-life: 36 months.
- **oral solution, 10 mg/ml.** Not in MEDL.

Ketoconazole

Ketoconazole was included in the 10th MEDL, but it has been replaced in the latest revision by fluconazole, which has a better therapeutic profile and reduced hepatic toxicity.

The tablet form is available as a generic in most markets. International distributors offer it and it is also included in the UNICEF list.

Use in HIV/AIDS: Treatment of oesophageal and resistant oropharyngeal candidiasis.

- **tablet, 200 mg.** Not in MEDL. Reported shelf-life: 36 months.
- **oral suspension, 100 mg/5 ml.** Not in MEDL.

Table 2. Sources and prices of antifungal drugs

ANTIFUNGALS	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Amphotericin B										
inj, 50 mg in vial	-	-	vial	-	-	-	-	-	5.20	2.28
Fluconazole										
cap/tab, 200 mg	7	5	cap/tab	7.25	0.20	0.36	0.24	2	13.35	5.92
inj, 2 mg/ml	1	1	100-ml	1.80	1.80	1.80	1.80	1	41.18	6.27
Itraconazole										
cap, 100 mg	2	2	cap	0.80	0.50	0.65	0.58	1	2.01	0.88
oral sol, 10 mg/ml	-	-	150-ml	-	-	-	-	-	73.53	48.07
Ketoconazole										
oral sol 100 mg/5ml	-	-	100ml	-	-	-	-	-	-	4.13
tab, 200 mg	3	3	tab	0.35	0.08	0.09	0.08	1	0.74	0.27

Explanatory notes to tables at the end of the document

Table 3. Drug cost associated with the treatment of cryptococcosis

CRYPTOCOCCOSIS. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Amphotericin B	inj 50 mg	0.8 mg/kg	1	14	14	2.28(a)	31.92	5.20	72.8
followed by fluconazole	cap 200 mg	400 mg	2	56	112	0.24	26.88	13.35	1495.2
							58.80		1568
Secondary prophylaxis									
fluconazole	cap 200 mg	200 mg	1	365	365	0.24	87.6	13.35	4872.75

Explanatory notes to tables at the end of the document

(a) Manufacturer's list price in Spain. No price was supplied by manufacturers

1.3. ANTIVIRAL DRUGS

Antiviral drugs are divided into two main groups: antiherpes drugs and antiretroviral (ARV) drugs.

ANTIHERPES DRUGS

Aciclovir

Aciclovir was one of the first antivirals added to the MEDL. Aciclovir was incorporated in the 1997 MEDL, in the therapeutic category of antiherpes agents. It has a very important role in HIV and STI for the treatment of severe primary genital herpes, disseminated herpes zoster and herpes encephalitis.

Patent expiry has opened up the market and the cost of a once very expensive drug has decreased considerably. Prices vary among different markets. There are numerous manufacturers of tablets, many with studies of bioequivalence to the original product. Indicated shelf-life varies among products. Dispersible tablets generally have a shorter shelf life than the tablet form and are more expensive. The majority of products on the market are tablets, and no distinction was made when comparing products. Aciclovir powder for injection, used in hospital settings for treatment of herpes encephalitis, is not as widely available as the tablet form. However, a number of generic products do exist.

Use in HIV/AIDS: Severe primary genital herpes, disseminated herpes zoster and herpes encephalitis.

Notes in 11th Model list: Limited indications or narrow spectrum of activity.

- **powder for injection, 250 mg (as sodium salt).** MEDL. Reported shelf-life: 24 to 60 months.
- **tablet, 200 mg.** MEDL. Reported shelf-life: 24 to 60 months.
- **tablet 400 mg,** Strength not in MEDL Reported shelf-life: 24 to 60 months
- **tablet, 800 mg.** Strength not in MEDL Reported shelf-life: 24 to 60 months.

Table 4. Sources and prices of antiviral (antiherpes) drugs

ANTIVIRALS Antiherpes	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Aciclovir										
inj, 250 mg	5	5	vial	13.58	2.58	3.30	2.70	2	-	4.38
tab, 200 mg	15	10	tab	2.81	0.04	0.10	0.06	4	0.60	0.41
tab, 400 mg	8	7	tab	2.51	0.09	0.14	0.12	2	0.86	-
tab, 800 mg	8	5	tab	4.07	0.20	0.48	0.25	2	3.74	1.36

Explanatory notes to tables at the end of the document

Table 5. Drug cost associated with the treatment of herpes simplex

HERPES SIMPLEX. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Aciclovir	tab 200 mg	1000 mg	5	5	25	0.06	1.5	0.60	15

Explanatory notes to tables at the end of the document

ANTIRETROVIRAL DRUGS

Abacavir, Didanosine, Efavirenz, Indinavir, Lamivudine, Nelfinavir, Nevirapine, Saquinavir, Stavudine, Zalcitabine, Zidovudine and the combination Zidovudine plus Lamivudine.

Presently, only two of the above are on the MEDL (1999), namely zidovudine and nevirapine. Both are included solely for the indication of reduction/prevention of mother-to-child transmission (MTCT) of HIV infection.

Currently available antiretroviral drugs belong to two major classes of drugs: reverse transcriptase inhibitors and protease inhibitors. The first is further divided into nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. These drugs act by blocking the action of enzymes that are important for replication and functioning of HIV.

Many of the antiretroviral drugs are not covered by patent in all countries. Therefore, there are a number of generic manufacturers producing these drugs. Some generic manufacturers only supply their national market and have not developed their capability for export, e.g. many of the Brazilian manufacturers.

Antiretroviral drugs used in MTCT and included in MEDL (1999):

Zidovudine (ZDV often called AZT)

Zidovudine is a nucleoside reverse transcriptase inhibitor. It was added to the tenth MEDL only for the indication of prevention or reduction of mother-to-child transmission. However, zidovudine is also used in combination therapy to suppress the replication of HIV.

Generic versions are widely available, as 100 mg and 250 mg capsules. The dosage used in prevention of MTCT is usually 300 mg.

Indicative prices vary widely depending on the country of origin of the product.

Use in HIV/AIDS: Prevention of MTCT (MEDL). Combination therapy to suppress replication of HIV.

Notes in 11th Model list: Limited indications or narrow spectrum of activity.

- **capsule, 100 mg.** MEDL. Reported shelf-life: 24 to 60 months
- **capsule, 250 mg.** MEDL. Reported shelf-life: 48 to 60 months
- **injection, 10 mg/ml in 20-ml vial.** MEDL. Reported shelf-life: 12 months
- **oral solution, 50 mg/5 ml.** MEDL. Reported shelf-life: 18 to 24 months
- **oral syrup, 10 mg/5 ml.** Strength not in MEDL
- **tablet, 300 mg.** Not in MEDL. Used in pilot projects for prevention of MTCT. Provided as a donation by Glaxo Wellcome to a restricted number of countries.

Nevirapine (NVP)

Nevirapine is a non-nucleoside reverse transcriptase inhibitor. This drug, used in combination therapy to suppress the replication of HIV, was included in the 1991 MEDL for the same indication as zidovudine (prevention of MTCT).

For this indication, a combination of tablet for the mother and syrup formulation for the new-born child is required. The indicative cost per treatment is 4 USD from the patent holder. However, recently the patent holder, Boehringer Ingelheim, has stated that the company will make the product available for MTCT free of charge to least developed and lower income developing countries with specific programmes on MTCT. Countries should approach the company directly for inclusion in this donation. The donation is only for MTCT and not to be used for combination therapy to suppress the replication of HIV.

Use in HIV/AIDS: Prevention of MTCT (MEDL). Combination therapy to suppress replication of HIV.

Notes in 11th Model list: Limited indications or narrow spectrum of activity.

- **tablet 200 mg.** MEDL.
- **oral solution 50 mg/ml (240 ml).** MEDL.

Antiretroviral drugs not included in MEDL (1999)

Combination ARV therapies reduce plasma viral load levels to undetectable levels and have a beneficial clinical effect. HIV-related symptoms may disappear, the incidence of opportunistic infections is reduced and quality of life improves. However, these treatments are not a cure for AIDS and have to be given for life or until it fails, or until they are superseded by new drug combinations.

For optimal efficacy, antiretroviral drugs, usually from different classes, must be used in combination. Several combination regimens with demonstrated effectiveness in achieving durable suppression of HIV replication are available.

The current ARV therapy is far from ideal. Some regimens are complicated, all may cause severe side effects and require close laboratory monitoring. In addition, the drugs are very costly.

Like most other drugs, ARV drugs are not covered by patents in all countries. They can therefore be legally produced and exported by generic manufacturers in countries where the products have not been patented, and can be legally imported and used in other countries where they have not been patented.

This survey of sources and prices has not been very successful as far as antiretrovirals are concerned. Only a few companies have responded and of those several supplied incomplete information. We have included only information from manufacturers that supplied us with all the information we requested (see page 2). Therefore, the information in table 6 gives an incomplete picture of the present status of the international market in generic antiretrovirals. On the other hand, we are reasonably sure that the drugs for which information is available

in the table are indeed available with reasonable quality assurances and at the prices stated. As this is a rapidly evolving field, we will make available to procurement officers contact information for manufacturers that supplied incomplete information, with a caveat that we have limited information on both the quality of their products or their ability to ensure a constant supply of their products. Other sources of prices of antiretroviral drugs include the web sites of the Brazilian AIDS Control Programme, of the Horizontal Technical Collaboration of Latin American AIDS control programmes, and of Boston University.

Abacavir

Abacavir is a nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **tablet 300 mg.** Not in MEDL.
- **syrup, 20 mg/ml.** Not in MEDL.

Didanosine (ddI)

Didanosine is a nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **tablet, 25 mg.** Not in MEDL.
- **tablet 100 mg.** Not in MEDL.
- **syrup, 2 g.** Not in MEDL.

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **capsule, 200 mg.** Not in MEDL.

Indinavir

Indinavir is a protease inhibitor used in combination therapy to suppress replication of HIV.

- **capsule, 400 mg.** Not in MEDL.

Lamivudine (3TC)

Lamivudine is a nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **tablet, 150 mg.** Not in MEDL.
- **syrup, 5 mg/ml.** Not in MEDL.

Nelfinavir

Nelfinavir is a protease inhibitor used in combination therapy to suppress replication of HIV.

- **capsule, 250 mg.** Not in MEDL.

Saquinavir

Saquinavir is a protease inhibitor used in combination therapy to suppress replication of HIV.

- **capsule, 200 mg.** Not in MEDL.

Stavudine (d4T)

Stavudine is a nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **capsule, 40 mg.** Not in MEDL.
- **syrup, 1 mg/ml.** Not in MEDL.

Zalcitabine (ddC)

Zalcitabine is a nucleoside reverse transcriptase inhibitor used in combination therapy to suppress replication of HIV.

- **tablet, 0.75 mg.** Not in MEDL.

Zidovudine plus Lamivudine (ZDV/3TC)

Fixed dose combination product containing two different nucleoside reverse transcriptase inhibitors that are often used in combination with a non-nucleoside reverse transcriptase inhibitors or HIV-protease inhibitors.

- **tablet, 300/150 mg.** Not in MEDL.

Table 6. Sources and prices of antiviral (antiretroviral) drugs

ANTIVIRALS <i>Antiretrovirals</i>	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Lamivudine										
tab, 150 mg	1	1	tab	0.89	0.89	0.89	0.89	1	3.83	1.96
syrup, 5 mg/ml	1	1	100 ml	5.85	5.85	5.85	5.85	1	-	-
Abacavir										
tab, 300 mg	-	-	tab	-	-	-	-	-	5.59	2.89
syrup, 20 mg/ml	-	-	240 ml	-	-	-	-	-	89.45	60.32
Zidovudine (AZT)										
cap, 100 mg	7	7	cap	0.30	0.18	0.28	0.24	2	1.68	0.47
cap, 250 mg	4	3	cap	0.75	0.50	0.66	0.55	1	4.20	1.18
cap, 300 mg	4	4	cap	1.00	0.28	0.64	0.52	1	5.03	1.41
syrup, 10 mg/5 ml	-	-		-	-	-	-	-	-	-
inj, 10 mg/ml, 20 ml	-	-	vial	-	-	-	-	-	16.85	-
oral sol, 50 mg/5 ml	1	1	100 ml	2.80	2.80	2.80	2.80	1	-	-
Stavudine										
syrup, 1 mg/ml	-	-	200 ml	-	-	-	-	-	34.25	14.27
cap, 40 mg	4	4	cap	0.85	0.30	0.40	0.36	1	4.32	1.68
Zalcitabine										
tab, 0.75 mg	-	-	tab	-	-	-	-	-	2.13	1.12
Didanosine										
tab, 25 mg	1	1	tab	0.19	0.19	0.19	0.19	1	0.67	0.20
tab, 100 mg	1	1	tab	0.61	0.61	0.61	0.61	1	2.06	0.79
syrup, 2 g	-	-	118 ml	-	-	-	-	-	-	15.74
ZDV/3TC comb										
tab, 300/150 mg	1	1	tab	No price					8.03	3.59
Efavirenz										
cap, 200 mg	-	-	cap	-	-	-	-	-	3.50	2.16
Nevirapine										
tab, 200 mg	1	1	tab	1.50	1.50	1.50	1.50	1	3.94	2.60
syrup, 50 mg/5 ml	-	-	240 ml	-	-	-	-	-	70.89	-
Indinavir										
cap, 400 mg	-	-	-	-	-	-	-	-	1.70	-
Nelfinavir										
cap, 250 mg	-	-	cap	-	-	-	-	-	1.51	0.81
Saquinavir										
cap, 200 mg	-	-	cap	-	-	-	-	-	0.78	0.75

Explanatory notes to tables at the end of the document

Table 7a. Example of drug cost for a the triple therapy regimen

AIDS Treatment (triple therapy) and duration (365 days)						Project estimates (25th percentile)		United Kingdom	
Treatment	Unit	Daily dose	Unit s/day	Day s	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Zidovudine	tab 300 mg	600 mg	2	365	730	0.52	379.6	5.03	3671.9
plus Lamivudine	tab 150 mg	300 mg	2	365	730	0.89	649.7	3.83	2795.9
plus Nelfinavir	cap 250 mg	2250 mg	9	365	3285	0.81(a)	2660.8	1.51	4960.3
							3690.1		11428.1

Table 7b. Example of drug cost for a the triple therapy regimen

AIDS Treatment (triple therapy) and duration (365 days)						Project estimates (25 th percentile)		United Kingdom	
Treatment	Unit	Daily dose	Units /day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Didanosine	tab 100 mg	400 mg	4	365	1460	0.61	890.6	2.06	3007.6
plus Stavudine	cap 40 mg	80 mg	2	365	730	0.36	262.8	4.32	3153.6
plus Nevirapine	tab 200 mg	400 mg	2	365	730	1.50	1095.0	3.94	2876.2
							2248.4		9037.4

Explanatory notes to tables at the end of the document

(a) Manufacturer's list price in Spain. No price was supplied by manufacturers

1.4. ANTIPROTOZOALS, ANTIPNEUMOCYSTOSIS AND ANTITOXOPLASMOSIS DRUGS

Pentamidine, Pyrimethamine, Calcium Folate (cytotoxic)

Pentamidine

To address the increasing problem of toxoplasmosis and infection with *Pneumocystis carinii* in immunosuppressed patients, the 1997 MEDL 1997 incorporated a new section dedicated to these agents. This section included pentamidine isetionate, pyrimethamine and sulfamethoxazole+trimethoprim. Pentamidine isetionate was previously included in the list as an antitrypanosomal drug (at 200 mg strength). The new strength included, 300 mg, is available from several manufacturers, however, in the present survey no replies were received. Two presentations exist, powder for injection and nebulizer. The 200 mg presentation is offered only by Rhône-Poulenc, and is available through WHO for trypanosomiasis programmes.

Use in HIV/AIDS: Prophylaxis of *Pneumocystis carinii* pneumonia (PCP), treatment of PCP in patients unable to tolerate first-line treatment.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 200 mg (isetionate) in vial.** MEDL.
- **powder for injection, 300 mg (isetionate) in vial.** MEDL. Reported shelf-life: 18 to 60 months.

Pyrimethamine

Pyrimethamine is an essential component of treatment regimes against *Toxoplasma gondii*. Pyrimethamine is available both as a generic from international suppliers and as a branded product (Glaxo Wellcome). While generic pyrimethamine tablets are available at a low cost, they are used in combination with calcium folinate (to reduce its toxicity) and sulfadiazine or clindamycin, and therefore adequate access to these drugs must also be secured.

Use in HIV/AIDS: Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis, treatment of isosporidiosis.

- **tablets, 25 mg.** MEDL.

Calcium folinate (cytotoxic drug)

Calcium folinate is included in the MEDL as a cytotoxic drug. However, it is an essential drug for the treatment and prophylaxis of toxoplasmosis, where it is used to reduce the toxicity of pyrimethamine. It is considered an expensive drug, and its price is a critical factor in the total drug cost of toxoplasmosis management.

Originally a product of Wyeth-Lederle, calcium folinate in tablets is available as a generic. While indicative prices varied widely, low cost sources were found.

Use in HIV/AIDS: To decrease the toxicity of pyrimethamine and other inhibitors of folic acid.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use (these precautions apply mainly in the context of chemotherapy with 5-fluorouracil, not for its use in HIV/AIDS).

- **tablet, 15 mg.** MEDL. Reported shelf-life: 24 to 36 months.

Table 8. Sources and prices of antipneumocystosis and antitoxoplasmosis drugs

ANTIPROTOZOALS (incl. Ca-folate)	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Pentamidine										
Inj, 200 mg (isetionate)	-	-	vial	-	-	-	-	-	-	-
inj, 300 mg (isetionate)	-	-	vial	-	-	-	-	-	46.05	10.74
Pyrimethamine										
tab, 25 mg	1	1	tab	0.003	0.003	0.003	0.003	1	0.10	0.06
Calcium folinate										
tab, 15 mg	2	2	tab	3.03	0.01	1.52	0.77	1	4.43	0.58

Explanatory notes to tables at the end of the document

Table 9. Drug costs associated with the treatment of toxoplasmosis

TOXOPLASMOSIS. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Pyrimethamine	tab 25 mg	100 mg	4	42	168	0.003	0.50	0.10	16.8
plus Sulfadiazine	tab 500 mg	6 g	12	42	504	0.02	10.08	0.44	221.76
plus Calcium folinate	tab 15 mg	15 mg	1	42	42	0.77	32.34	4.43	186.06
							42.92		424.62
Secondary prophylaxis									
Pyrimethamine	tab 25 mg	25 mg	1	365	365	0.003	1.095	0.10	36.5
plus Sulfadiazine	tab 500 mg	3 g	6	365	2190	0.02	43.8	0.44	963.6
plus Calcium folinate	tab 15 mg	15 mg	1	365	365	0.77	281.05	4.43	1616.95
							325.95		2617.05

Explanatory notes to tables at the end of the document

2. DRUGS USED IN HIV/AIDS RELATED MALIGNANCIES

2.1. CYTOTOXIC DRUGS

This survey of sources and prices has not been very successful as far as cytotoxic drugs are concerned. Only few companies responded and of those several supplied incomplete information. In the 1999 survey we had a much better response and therefore we will make available to procurement officers, on request, contact information from the 1999 survey, with a caveat that this information may be outdated.

Bleomycin, Doxorubicin, Methotrexate, Vinblastine and Vincristine

Bleomycin

Generic bleomycin injection is available from manufacturers specializing in cytotoxics. In the 1999 survey, 7 manufacturers responded and prices from different manufacturers varied widely. However, in the present survey no manufacturer replied. The drug is on the list of one international supplier.

Main use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 15 mg (as sulfate) in vial.** MEDL. Reported shelf-life: 18 to 24 months.

Doxorubicin

Doxorubicin is offered by the main companies that specialize in oncology drugs, however only one of these responded to the 2000 survey. While the powder for injection is the more usual form available, in developed countries the drug is also offered as a solution for injection. The lyophilised formulation is easier to store than the solution, which requires refrigeration.

Use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 10 mg in vial.** MEDL. Reported shelf-life: 18 to 36 months.
- **powder for injection, 50 mg in vial.** MEDL. Reported shelf-life: 18 to 36 months.

Methotrexate

Methotrexate is widely available on the generic market, especially in tablet form. The formulations included in the MEDL are powder for injection 50 mg and tablets 2.5 mg. Generic manufacturers and international suppliers also offer the solution for injection, 2.5 mg/ml in 2-ml vial.

Use in HIV/AIDS: AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 50 mg (as sodium salt) in vial.** MEDL. Reported shelf-life: 24 months.
- **injection, 25 mg (as sodium salt)/ml in 2-ml vial.** MEDL (alternative formulation). Reported shelf-life: 24 to 36 months.
- **tablet, 2.5 mg.** MEDL. Reported shelf-life: 24 to 36 months.

Vinblastine

The drug is available as powder for injection or solution for injection from various manufacturers but none of these responded to the present survey. Both formulations require refrigeration.

Use in HIV/AIDS: Kaposi's sarcoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 10 mg (sulfate) in vial.** MEDL. Indicated shelf-life: 18 to 36 months. REFRIGERATION REQUIRED.
- **injection, 1 mg (sulfate)/ml in 10-ml vial.** MEDL (alternative formulation). Reported shelf-life: 18 to 36 months. REFRIGERATION REQUIRED.

Vincristine

As with vinblastine, vincristine is available from generic manufacturers and international distributors but we have had limited response. Two presentations are available, powder for injection and solution for injection. The powder for injection is listed in the MEDL. Both must be kept refrigerated.

Use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 1 mg (sulfate) in vial.** MEDL. Reported shelf-life: 24 to 30 months. REFRIGERATION REQUIRED.

Table 10. Sources and prices of cytotoxic drugs

CYTOTOXICS	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Bleomycin										
inj, 15 mg in vial	-	-	vial	-	-	-	-	-	22.91	8.00
Doxorubicin HCl										
pdr inj, 10 mg in vial	1	1	vial	14.65	14.65	14.65	14.65	1	26.33	4.33
pdr inj, 50 mg in vial	1	1	vial	70.43	70.43	70.43	70.43	1	131.65	19.30
Methotrexate										
pdr inj, 50 mg in vial	1	1	vial	4.25	4.25	4.25	4.25	1	-	2.82
tab, 2.5 mg	2	2	tab	0.14	0.04	0.09	0.06	1	0.20	0.04
Vinblastine										
pdre inj, 10 mg	-	-	vial	-	-	-	-	-	19.90	-
inj, 10 mg in vial	1	1	2 ml	4.70	4.70	4.70	4.70	1	18.41	5.14
Vincristine										
pd inj 1 mg (sulfate) in vial	1	1	vial	3.35	3.35	3.35	3.35	1	-	-
pd inj 5 mg (sulfate) in vial	-	-	vial	-	-	-	-	-	-	-
inj, 5 mg	-	-	vial	-	-	-	-	-	62.11	15.06

Explanatory notes to tables at the end of the document

Table 11. Drug costs associated with the treatment of Kaposi's sarcoma

KAPOSI'S SARCOMA. Treatment and duration (5)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Bleomycin	inj 15 mg	15 mg/m ² (6 cycles)			12	8.00(a)	96	22.91	274.92
plus Vincristine	inj 1mg	2 mg (6 cycles)			12	3.35	40.2	17.53 (a)	210.36
							136.2		485.28

Explanatory notes to tables at the end of the document

(a) Manufacturer's list price in Spain (in 1999 for Vincristine). No price was supplied by manufacturers

3. DRUGS USED IN PALLIATIVE CARE

3.1. OPIOID ANALGESICS

Codeine phosphate, Methadone, Morphine, Pethidine

While opioid analgesics, including methadone for management of drug addiction, are essential components in palliative care for HIV/AIDS, the availability of drugs and range of formulations is limited in developing countries. This is partly due to regulatory constraints that affect the supply and usage of these drugs, and which especially affect countries where there is no local production.

International supply of opioid analgesics is limited to the more commonly used products (codeine tablets, morphine injection and pethidine injection). International suppliers and UNICEF include at least one of them in their product lists.

The drugs included in this section are all controlled substances under the Single Convention on Narcotic Drugs, 1961. Manufacturers require special authorization from the importing country before an export license is granted, and due to regulatory constraints, batch samples are not available for evaluation.

Codeine

Use in HIV/AIDS: Treatment of mild to moderate pain, symptomatic relief of diarrhoea.

Notes in 11th Model list: Example of a therapeutic group. Drug subject to international control.

- **tablet, 30 mg.** MEDL. Reported shelf-life: 36 months.

Methadone

Methadone is available in oral formulations (tablets and mixture) and in ampoules for injection. The more common form used in drug dependence are oral liquid formulations.

Use in HIV/AIDS: Management of opioid dependence.

- **Methadone, tablet, 5 mg.** Not in MEDL.

Morphine

Use in HIV/AIDS: Treatment of severe pain.

Notes in 11th Model list: Example of a therapeutic group. Drug subject to international control.

- **oral solution, 10 mg (hydrochloride or sulfate)/5 ml.** MEDL.
- **tablet, 10 mg (sulfate).** MEDL.

Pethidine

Use in HIV/AIDS: Treatment of severe pain.

Notes in 11th Model list: Example of a therapeutic group. Complementary drug. Use when drugs in the main list cannot be made available. Drug subject to international control. In renal insufficiency, contraindicated or dosage adjustments necessary.

- **inj, 50 mg (hydrochloride) in 1-ml ampoule.** MEDL. Reported shelf-life: 18 to 36 months.
- **tablet, 50 mg.** MEDL. Reported shelf-life: 24 months.
- **tablet, 100 mg.** MEDL.

Table 12. Sources and prices of opioid analgesics

ANALGESIC (OPIOID)	Manuf. (1)		Indicative prices (USD, 2000) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Codeine										
tab, 30 mg	3	3	tab	0.05	0.03	0.04	0.04	2	-	0.08
Methadone										
tab, 5 mg	1	1	0.04	0.04	0.04	0.04	0.04	1	0.09	0.03
Morphine										
oral sol HCl 10 mg/5 ml	1	1	200 ml	10.47	10.47	10.47	10.47	1	-	-
oral sol sulf 10 mg/5 ml	-	-	500 ml	-	-	-	-	-	11.73	-
tab, 10 mg sulfate	1	1	tab	0.09	0.09	0.09	0.09	1	0.15	0.13
Pethidine										
inj, HCl 50 mg/ml	1	1	vial	0.24	0.24	0.24	0.24	1	0.75	0.45
tab, 100 mg	-	-	amp	-	-	-	-	-	-	-
tab, 50 mg	-	-	tab	-	-	-	-	-	0.14	-

Explanatory notes to tables at the end of the document

Notes to tables

- (1) Number of manufacturers that provided indicative prices and countries of origin.
- (2) As indicated by manufacturers. Prices are ex-works or FOB, and do not include freight, insurance or taxes. Range, median, 25th percentile and number of products with price equal to or below the 25th percentile are indicated. Exchange rates to USD vary (period between July and November 1999).
- (3) Spanish price is the manufacturer's price as of September 2000, calculated from public prices indicated in Base de Datos del Medicamento del Consejo General de Colegios Farmacéuticos de España (www.cof.es). Prices indicated for the United Kingdom are those set by the NHS for reimbursement (British National Formulary 39, March 2000). Lowest price is indicated. Rates: 1 USD= 193.546 ESP; 1 USD= 0.711 GBP.
- (4) Examples of treatments. Source: *Standard treatments and essential drugs for HIV-related conditions*. WHO, 1997. (DAP/97.9).
- (5) The treatment indicated for Kaposi's Sarcoma is an example of BV therapy (Gill P *et al.* 1990. *American Journal of Clinical Oncology*, 13(4), 315–9).
- (6) Treatment indicated for HIV is taken from *Guidance Modules on Antiviral Treatments, Module 4*. WHO/UNAIDS, 1998. (WHO/ASD/98.1 – UNAIDS/98.7).

Materials

UNAIDS (1998). *Access to drugs: UNAIDS Technical Update*. Geneva, UNAIDS.

UNAIDS (1998). *HIV-related opportunistic diseases: UNAIDS Technical Update*. Geneva, UNAIDS.

WHO (1997). *Standard treatments and essential drugs for HIV-related conditions*. Geneva, WHO. (DAP/97.9).

WHO (1999). Essential drugs: WHO Model List (revised December 1999). *WHO Drug Information*, 13(4): 249–262.

WHO (1999). *WHO Model prescribing information: Drugs used in HIV-related infections*. Geneva, WHO. (WHO/DMP/DSI/99.2).

WHO/UNAIDS/IAS International Society (2000). *Safe and effective use of antiretroviral treatments in adults, with specific references to resource limited settings*. Geneva, WHO. (WHO/HIS/2000.04).

UNAIDS: www.unaids.org

UNICEF: www.unicef.org

WHO: www.who.int

Contacts

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